
Asecretory POEMS Syndrome with Widespread Osteosclerotic Lesions

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ABSTRACT

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) is a rare disease and constitutes 1-2% of plasma cell dyscrasia. Most of the patients have few sclerotic bone lesions and more than 90% of patients have serum and/or urinary M-protein. In this report, we present a patient with POEMS syndrome who had severe polyneuropathy and unusual widespread osteosclerotic lesions without M-protein in serum and urine. According to our knowledge, this is the first case of asecretory POEMS syndrome with multiple sclerotic lesions and polyneuropathy. Our patient is still well and able to work actively 4 years after diagnosis with the treatment of 12 courses of VAD by reducing the vincristine dosage.

Key Words: POEMS syndrome, Asecretory, Osteosclerosis.

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INTRODUCTION

POEMS syndrome is a rare form of plasma cell dyscrasia that is characterised by polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes^[1,2]. Although POEMS is an acronym referring to the major features, the patients may have some other associated findings including papilledema, lymphadenopathy, hepatosplenomegaly, peripheral edema, renal dysfunction and osteosclerotic lesions. The certain underlying mechanisms of POEMS are not completely understood. It has been suggested that the manifestations of POEMS syndrome might be regarded as the result of a marked activation of the proinflammatory cytokine network (IL-1b, IL-6 and TNF-a) associated with a weak or even decreased TGFb1 antagonistic re-

action^[3]. An overproduction of the vascular endothelial growth factor (VEGF) might be an important consideration in the pathogenesis of this disorder^[4]. Also, the determination of association with the human herpes virus-8 (HHV-8) infection and POEMS syndrome-associated multicentric Castleman's disease indicates that there is a relationship between POEMS syndrome and HHV-8^[5]. Osteosclerotic bone lesions are usually focal and local therapy can control disease manifestations successfully.

CASE

A 36 year old man was admitted in August 1996 to the outpatient unit with the complaints of progressive difficulty in walking, a loss of strength, tingling sensation of the hands and weight loss. Physical examinati-

on revealed hyperpigmentation of the skin, a right axillary lymphadenopathy (2x1 cm) and hepatosplenomegaly (3 cm below costal margin), loss of deep tendon reflexes, quadriplegia which was more marked in the lower extremities with a stocking-glove distribution of sensory loss and paresthesia. The patient was almost totally bedridden. He also had bilateral papilloedema.

The laboratory examination revealed: Hemoglobin concentration: 12 g/dL, hematocrit 34% (normochromic, normocytic red cells), WBC 6800/mm³ and platelet count 519.000/mm³. The peripheral blood smear, differential count and urinary analysis were all normal. Biochemical analysis revealed serum albumin 2.9 g/dL, globulin 3.3 g/dL, fasting blood sugar level of 154 mg/dL and 156 mg/dL on two consecutive days, a postprandial blood sugar level of 212 mg/dL. Serum testosterone level was lower than normal. There was no monoclonal gammopathy in serum and urine protein electrophoresis and no Bence-Jones proteinuria, serum gamma globulin fraction was also normal as the levels of serum immunoglobulins. A monoclonal band could

not be detected by neither serum nor urine immunofixation (Minifix) studies. EMG showed severe mixed type polyneuropathy, predominantly in lower extremities with both axonal degeneration and segmental demyelination. Multiple sclerotic lesions were seen at the sacrum, the left ileum and the left sacroiliac joint on plain X-ray (Figure 1). The sclerotic lesions were also found in some isolated vertebrae by MRI (Figure 2). An abdominal ultrasound revealed a hepatosplenomegaly without tumoral mass or hemangioma. A cranial CT which was done for papilloedema was found to be within normal limits.

The first bone marrow aspiration and biopsy were normocellular without any increase in the plasma cells. On the 2nd trial, bone marrow aspiration was found to be hypercellular and had which a plasma cell concentration of 7% at focal areas, some of which showed obvious atypical changes. A trough-cut bone biopsy, was done from the osteosclerotic lesion in the left ileum, also failed to demonstrate plasma cell infiltration. A second, but deeper, bone marrow biopsy was attempted



Figure 1. The osteosclerotic bone lesions of sacrum and ileum on X-ray



Figure 2. The osteosclerotic bone lesions on T12, L1 and S1 vertebrae and sacrum with MRI scanning

since the findings strongly suggested POEMS syndrome.

DISCUSSION

We present a case of asecretory POEMS syndrome with multiple osteosclerotic lesions in contrast to the commonly seen solitary lesion. The patient had typical clinical findings of POEMS syndrome, but no detectable serum or urine monoclonal protein. Through-cut bone biopsy did not yield satisfactory amounts of material. Since the findings strongly suggested POEMS syndrome, a second but deeper bone marrow biopsy was attempted. This was successful and pathological examination microscopically revealed an islet of atypical plasma cells demonstrating diffuse cytoplasmic reactivity with anti-lambda monoclonal antibodies (Figure 3). No positivity was recorded on slides stained for anti-kappa antibodies, providing evidence for the monoclonal nature of the plasma cell population. The biopsy of a lymph node from the right axillary fossa to rule out lymphoma was reported as "reactive".

Polyneuropathy is a prominent feature of POEMS syndrome, and is usually of the mixed sensorimotor type, motor components being more marked, which is also true for the presented patient^[6]. It frequently begins at the lower extremities and spreads to the upper extremities leading to severe motor deficits as in this presented case. A sural nerve biopsy usually demonstrates axonal degeneration and sometimes segmental demyelination^[1]. In this reported case we have found the same features by EMG. The cause of neuropathy is not clear, but the presence of antineuronal antibodies points to an immunological mechanism^[7]. There is no relation between the levels of M-protein and the severity of the polyneuropathy^[8]. In this case, the occurrence of severe polyneuropathy in the absence of monoclonal gammopathy supports this finding.

Increased vascular endothelial growth factor (VEGF) as causative in Crow-Fukase syndrome has suggested that vascular endothelial growth factor affects blood nerve barrier and increases microvascular permeability, thereby inducing endoneurial edema. Serum components such as complement and trombins, which are toxic to the nerves, may induce nerve damage^[4].

Papilledema may be seen in approximately 37% of patients and is not associated with the increase in intracranial pressure^[9]. The real cause of papilledema is

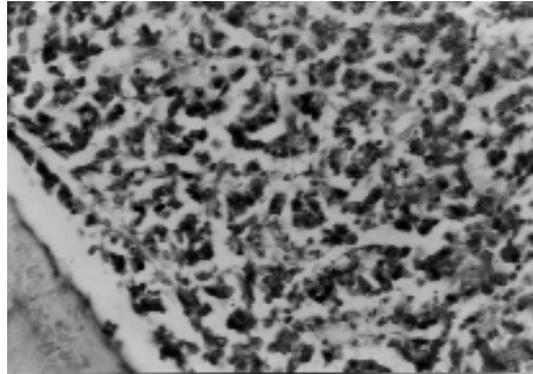


Figure 3. Dutcher bodies and cytoplasmic immunoreactivity with anti-lambda antibody (streptavidin-biotin peroxidase x40)

not still known. Hepatomegaly, differing from multiple myeloma, may be seen in up to 50% of patients of POEMS syndrome, with splenomegaly and lymphadenopathy occurring less often^[1,10].

Endocrinological abnormalities may be seen in POEMS syndrome with a frequency of 60-80%, the most common of which are gonadal failure (70%) and glucose intolerance/diabetes mellitus (50%)^[1,11]. In addition, low plasma testosterone levels together with testicular atrophy, impotence and gynecomastia can be seen in male patients. Hypo or hyperthyroidism, hyperprolactinemia and adrenal insufficiency have also been reported^[12]. The mechanism of endocrinopathy is not obvious however; there are some studies demonstrating directly acting antibodies against hypothalamo-hypophyseal axis and endocrine end organs^[13]. In the reported patient, the complaint of impotence, low testosterone levels and the absence of diabetes in his family story drew our attention.

Monoclonal protein is detected in more than 90% of patients and may become positive in the follow-up of patients who have no monoclonal gammopathy initially^[10]. Nearly all cases reported in the literature show lambda positivity. M-protein may also be rarely found in the urine. In the present case, another urine and serum immunofixation electrophoresis did not show M-protein, even three years after the diagnosis.

This case is reported because of multiple osteosclerotic lesions without serum M-protein and the demonstrated lambda positive plasma cells in bone marrow biopsy, and the widespread osteosclerotic bone

lesions. The patient has received twelve courses of VAD chemotherapy (reduced vincristine dosage). There has been no improvement in the bone lesions radiologically. On the other hand, neurological findings have shown a marked clinical recovery. Although the median survival time of such patient was reported to be less than one year, our patient is able to work without support after the 48th month of diagnosis. He is still under follow up.

REFERENCES

1. Nakanishi T, Sobue I, Toyokura Y, Nishitani H, Kuroiwa Y, Satoyoshi E, Tsubaki T, Igata A, Ozaki Y. The Crow-Fukase syndrome: A study of 102 cases in Japan. *Neurology* 1984;34:712-20.
2. Piette WW. Myeloma, paraproteinemias and the skin. *Med Clin North Am* 1986;70:155-76.
3. Gherardi RK, Belec L, Soubrier M, Malapert D, Zuber M, Viard JP, Intrator L, Degos JD, Authier FJ. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. *Blood* 1999;87(4):1458-65.
4. Watanabe O, Maruyama I, Arimura K, Kitajawa I, Arimura H, Hanatani M, Matsuo K, Arisato T, Osawa M. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. *Muscle Nerve* 1998;21(11):1390-7.
5. Belec L, Mohamed AS, Archier FS, Hallouin MC, Soe AM, Cotigny S, Gaulard P, Gherardi RK. Human herpesvirus 8 infection in patients with POEMS syndrome associated multicentric Castleman's disease. *Blood* 1999; 1;93(11):3643-53.
6. Kelly JJ Jr, Kyle RA, Miles JM, O'Brian PC, Dyck PJ. The spectrum of peripheral neuropathy in myeloma. *Neurology* 1981;31:31-4.
7. Reulecke MD, Dumas M, Merrier C. Specific antibody activity against neuroendocrine tissue in a case of POEMS syndrome with IgG gammopathy. *Neurology* 1988;38:614-6.
8. Miralles GD, O'Fallen JR, Talley NJ. Plasma cell dyscrasia with polyneuropathy; The spectrum of POEMS syndrome. *N Eng J Med* 1992;327:1919-23.
9. Trentham DE, Maji AT, Marker HW. Polyneuropathy and anasarca: Evidence for a new connective tissue syndrome and vasculopathic contribution. *Ann Intern Med* 1976;84:271-27.
10. Driedger H, Pruzanski W. Plasma cell neoplasia with peripheral neuropathy; a study of five cases and a review of the literature. *Medicine* 1980;59:301-10.
11. Waldenström JG, Adner A, Gydell K, Zetterwall O. Osteosclerotic plasmacytoma with polyneuropathy, hypertrichosis and diabetes. *Acta Med Scand* 1978;203:297-303.
12. Vidakovic A, Simic P, Stojisavljevic N, Elezovic Ivo, Trikić R, Apostoloski S. Polyneuropathy with osteosclerotic myeloma-POEMS syndrome. *J Neurol* 1992;239:49-52.
13. Kelly JJ Jr, Kyle RA, Miles JM, Dyck PJ. Osteosclerotic myeloma and peripheral neuropathy. *Neurology* 1993;33:202-10.

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